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The World Health Organization (WHO) classification of tumors of the hematopoietic and lymphoid tissues: An overview with emphasis on the myeloid neoplasms

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ABSTRACT

The World Health Organization (WHO) classification of myeloid and lymphoid neoplasms utilizes morphology, immunophenotype, genetics and clinical features to define disease entities of clinical significance. It is a consensus classification in which a number of experts have agreed on the classification and diagnostic criteria. In general, the classification stratifies neoplasms according to their lineage (myeloid, lymphoid, histiocytic/dendritic) and distinguishes neoplasms of precursor cells from those comprised of functionally mature cells. Lymphoid neoplasms are derived from cells that frequently have features that recapitulate stages of normal B-, T-, and NK-cell differentiation and function, so to some extent they can be classified according to the corresponding normal counterpart, although additional features, such as genotype, clinical features and even location of the tumor figure into the final classification listing as well. Five major subgroups of myeloid neoplasms are recognized based mainly on their degree of maturation and biologic properties: myeloproliferative neoplasms (MPNs) which are comprised primarily of mature cells with effective proliferation; myeloid (and lymphoid) neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB* and *FGFR1*, defined largely by the finding of significant eosinophilia and specific genetic abnormalities; myelodysplastic/myeloproliferative neoplasms (MDS/MPN), comprised mainly of mature cells with both effective and ineffective proliferation of various lineages; myelodysplastic syndromes (MDS), in which immature and mature cells are found with abnormal, dysplastic and ineffective maturation, and acute myeloid leukemia (AML), comprised of precursor cells with impaired maturation. Genetic abnormalities play an important role as diagnostic criteria for further subclassification of some myeloid neoplasms, particularly of AML. Although therapy-related MDS and AML (t-MDS/AML) often have genetic defects identical to those found in de novo AML and de novo MDS, they are classified separately from de novo AML and MDS in order to emphasize their unique clinical and biologic properties.

1. Introduction and background

An ideal classification scheme of hematopoietic malignancies should include diseases that are clinically significant, clearly defined, mutually exclusive of each other, and that can be diagnosed using currently available technology and information. In addition, there should be general consensus and acceptance of the classification for it to be useful for daily clinical practice as well as for scientific investigations. Lastly, the classification should be flexible and changeable as new information accumulates. In 2001, the World Health Organization (WHO), in collaboration with the Society for Hematopathology and the European Association of Hematopathology, attempted to meet these goals and published a classification of Tumors of the Hematopoietic and Lymphoid Tissues as part of the 3rd edition of the series, *WHO Classification of Tumors* [1]. In 2008, the classification was updated and published as part of the 4th edition of the WHO monograph series [2]. The aim of the revision was to incorporate new scientific and clinical information that has accumulated since the previous edition in order to refine diagnostic criteria for previously described neoplasms and to introduce newly recognized disease entities.

1.1. Principles of the WHO classification

The principles of the WHO classification have been previously described [3–5]. The major principle is that the classification relies on a combination of clinical, morphologic, immunophenotypic, genetic and other biologic features to define specific disease

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entities—a logical approach similar to that followed by a clinician and pathologist as they work together to reach a diagnosis for a patient suspected to have a hematopoietic neoplasm. The relative contribution of each of these parameters to the final diagnosis varies depending on the disease entity. For some neoplasms, morphology alone may be sufficient for classification, but in others, knowledge of the genetic lesion is necessary for the final diagnosis and classification, and often for the treatment as well. Although perhaps overused as a prototype for the identification and classification of hematopoietic neoplasms, chronic myelogenous leukemia (CML) serves as a good example of the approach and goal of the WHO classification for an individual disease. CML is mainly recognized by its clinical and morphologic features, but is consistently associated with a specific genetic defect, the *BCR-ABL1* fusion gene, that results in the production of a constitutively activated tyrosine kinase (TK) that in turn activates a number of different cellular pathways to influence proliferation, survival and differentiation of the neoplastic cell. The protein provides a target for TK inhibitor therapy that has prolonged the lives of thousand of patients with CML [6]. However, the diagnosis of CML is not made on any single parameter—there are other disorders that can mimic its clinical presentation and morphology, and the *BCR-ABL1* gene is found in cases of acute lymphoblastic leukemia and mixed phenotype acute leukemia as well as in CML. Thus, CML is an excellent example of the integration of all pieces of relevant information into the definition of a disease entity.

A second principle of the classification is that there should be agreement on the diagnostic criteria, nomenclature and classification among a number of experts in the field. Key to the development of the 4th edition was the input of approximately 70 internationally recognized clinicians and clinical scientists who met with the pathologists to discuss the merits of the proposed classification scheme and the revisions. Eventually, over 150 hematopathologists, clinical hematologists and scientists participated in the final development and writing of the 4th edition of the *WHO Classification of Tumors of the Hematopoietic and Lymphoid Tissues*.

2. The WHO classification of hematopoietic and lymphoid tumors, general features

The complete WHO classification is listed in Table 1. Perusal of the table reveals that the hematopoietic neoplasms are stratified broadly according to the lineage of the neoplastic cells, i.e., myeloid, lymphoid, histiocytic/dendritic, or ambiguous lineage. The latter category is comprised of precursor cell neoplasms (acute leukemia) that are comprised of cells that lack any specific lineage-associated markers and are thus "undifferentiated," or that express antigens of more than one lineage, and thus appear to have a mixed lineage phenotype [7,8]. Neoplasms comprised of precursor cells (acute myeloid leukemia, lymphoblastic leukemia/lymphoma, blastic plasmacytoid dendritic cell neoplasm, and acute leukemia of ambiguous lineage) are considered separately from those comprised of more mature cells (myeloproliferative neoplasms, myelodysplastic/myeloproliferative neoplasms, myelodysplastic syndromes, mature B-cell and T/NK-cell lymphoma, Hodgkin lymphoma and histiocytic/dendritic cell neoplasms). For the mature lymphoid neoplasms, further sub-classification and listing is based to some extent on the stage of differentiation as compared to a postulated normal counterpart (e.g., mantle cell lymphoma, follicular lymphoma), on morphology (e.g., diffuse large B cell lymphoma), on clinical presentations or the clinical setting (e.g., diffuse large B cell lymphoma associated with chronic inflammation), or more commonly, on the combination of morphologic, immunophenotypic and/or genetic parameters that together allow a specific disease entity to be defined (e.g., Anaplastic large cell lymphoma, ALK pos-

Table 1
WHO classification of hematopoietic and lymphoid neoplasms.

- Myeloproliferative neoplasms
  - Chronic myelogenous leukaemia, *BCR-ABL1* positive
  - Chronic neutrophilic leukaemia
  - Polycythaemia vera
  - Primary myelofibrosis
  - Essential thrombocythaemia
  - Chronic eosinophilic leukaemia, NOS
  - Mastocytosis
    - Cutaneous mastocytosis
    - Systemic mastocytosis
    - Mast cell leukaemia
    - Mast cell sarcoma
    - Extracutaneous mastocytoma
  - Myeloproliferative neoplasm, unclassifiable
- Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB or FGFR1*
  - Myeloid and lymphoid neoplasms with *PDGFRA* rearrangement
  - Myeloid neoplasms with *PDGFRB* rearrangement
  - Myeloid and lymphoid neoplasms with *FGFR1* abnormalities
- Myelodysplastic/myeloproliferative neoplasms
  - Chronic myelomonocytic leukaemia
  - Atypical chronic myeloid leukaemia, *BCR-ABL1* negative
  - Juvenile myelomonocytic leukaemia
  - Myelodysplastic/myeloproliferative neoplasm, unclassifiable
  - *Refractory anaemia with ring sideroblasts associated with marked thrombocytosis*
- Myelodysplastic syndromes
  - Refractory cytopenia with unlineage dysplasia
    - Refractory anaemia
    - Refractory neutropenia
    - Refractory thrombocytopenia
  - Refractory anaemia with ring sideroblasts
  - Refractory cytopenia with multilineage dysplasia
  - Refractory anaemia with excess blasts
  - Myelodysplastic syndrome associated with isolated del(5q)
  - Myelodysplastic syndrome, unclassifiable
  - Childhood myelodysplastic syndrome
    - *Refractory cytopenia of childhood*
- Acute myeloid leukaemia (AML) and related precursor neoplasms
  - AML with recurrent genetic abnormalities
    - AML with t(8;21)(q22;q22), *RUNX1-RUNX1T1*
    - AML with inv(16)(p13.1q22) or t(16;16)(p13.1;p22); CBFB-MYH11
    - Acute promyelocytic leukaemia with t(15;17)(q22;q12);PML-RARA
    - AML with t(9;11)(p22;q23)MLLT3-MLL
    - AML with t(6:9)(p23;q34); DEK-NUP214
    - AML with inv(3)(q21q26.2) or t(3.3)(q21;q26.2); RPN1-EVl1
    - AML (megakaryoblastic) with t(1:22)(p13;q13); RBM15-MKL1
    - AML with mutated NPM1
    - AML with mutated CEBPA
- AML with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- Acute myeloid leukaemia, NOS
  - AML with minimal differentiation
  - AML without maturation
  - AML with maturation
  - Acute myelomonocytic leukaemia
  - Acute monoblastic and monocytic leukaemia
  - Acute erythroid leukaemia
  - Acute megakaryoblastic leukaemia
  - Acute basophilic leukaemia
  - Acute panmyelosis with myelofibrosis
- Myeloid sarcoma
- Myeloid proliferations related to Down syndrome
  - Transient abnormal myelopoiesis
  - Myeloid leukaemia associated with Down syndrome
- Blastic plasmacytoid dendritic cell neoplasm
- Acute leukaemias of ambiguous lineage
  - Acute undifferentiated leukaemia
  - Mixed phenotype acute leukaemia with t(9;22)(q34;q11.2); *BCR-ABL1*
  - Mixed phenotype acute leukaemia with t(v;11q23); *MLL* rearranged
  - Mixed phenotype acute leukemia, B/myeloid, NOS
  - Mixed phenotype acute leukaemia, T/myeloid, NOS
  - *Natural killer (NK) cell lymphoblastic leukaemia/lymphoma*